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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,324	LARSEN ET AL.	
	Examiner	Art Unit	
	Robert T. Crow	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *87-140* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *87-140* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/4/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

Status of the Claims

1. This action is in response to papers filed 4 May 2010 in which claims 87 and 108 were amended, no claims were canceled, and no new claims were added. All of the amendments have been thoroughly reviewed and entered.

The previous rejections under 35 U.S.C. 112, second paragraph, not reiterated below are withdrawn in view of the amendments. Applicant's arguments have been thoroughly reviewed and are addressed following the rejections.

The previous rejections under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) not reiterated below are withdrawn in view of the amendments. Applicant's arguments have been thoroughly reviewed and are addressed following the rejections necessitated by the amendments.

Claims 87-140 are under prosecution.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 87-140 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 87-140 are indefinite in claim 87, which recites "the sample" in lines 18-19 of claim 87. The recitation of "the sample" lacks antecedent basis because the claim does not previously recite a sample. It is suggested that the claim be

amended to reflect proper antecedent basis. This is a new rejection necessitated by the amendments.

B. Claims 139 and 139 contain the trademark/trade names Cy3, Cy5, ad Cy5.5. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe chemical structures and, accordingly, the identification/description is indefinite. This rejection is maintained from the previous Office Action.

4. The following rejections are new rejections necessitated by the amendments.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 87-92, 95-99, 101-102, 107-108,110, 112, 114, 116-118, 120-127, 129-130, and 137-140 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) in view of in view of Kaplan (U.S. Patent No. 6,280,961 B1, issued 28 August 2001) and, as applied to claim 91 as evidenced by Smith et al (J. Exp. Med., vol. 178, pages 2035-2046 (1 December 1993)).

Regarding claim 87, Hansen et al teach a method for assessing at least one quality parameter of a particle in a liquid material (Abstract); namely, the particles are red blood cells in a liquid material (paragraph 0007). Page 9 of the instant specification recites blood cells as a preferred form of particle. Thus, the blood cells of Hansen et al are particles that have bound thereto or comprised therein less that $1x10^6$ analyte detectable positions per particle, and the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding "analytes in an

amount of less than $1x10^6$ analyte detectable positions per particle" (*In re Hyatt*, 211 F.3d1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) (see MPEP 2111 [R-1]). The liquid material (i.e., sample) is mixed with (i.e., via addition of) with a labeling agent, in the form of coloring molecules, which emits radiation in the form of fluorescence to result in the generation of a detectable electromagnetic signal (i.e., the fluorescence; paragraphs 0048-0049). A volume of the liquid material (i.e., the mixture) is arranged in a sample compartment having a wall defining an exposing area, wherein the wall allows a signal to pass through the wall to the exterior; i.e., to an array of detection elements paragraph 0019). The detectable electromagnetic signal is the fluorescence (paragraphs 0048-0049).

Hansen et al also teach a representation of the electromagnetic signals from the labeling agent that have passed through the wall is exposed to an array of active detection elements (paragraph 0020). The ratio of a linear dimension of the image on the array of detection elements to the original linear dimension in the exposing domain is small than 20:1; namely, the enlargement ratio is at most 20:1 (paragraph 0064). Hansen et al teach a plurality of particles is detected simultaneously (paragraphs 0034 and 0225), and that the representation is detected as intensities on individual active detection elements (paragraphs 0017 and 0020). Representations of electromagnetic signals for the particles are processed as distinct from background (Abstract). Hansen et al further teach the particles and sample are detected at a standstill during the exposure (paragraph 0070), and at least one quantity or quality parameter is assessed (Abstract).

While Hansen et al also teach the biological particles (i.e., cells) are bound to a reagent material comprising a first targeting species in the form of beads having components in connection with assessment of biomolecules (i.e. in the cells; paragraph 0379), that the particles are retained magnetically (paragraph 0234), and that more than one reagent is mixed with the analyte (paragraph 0240), Hansen et al do not explicitly teach the first targeting species (magnetic bead) and labeling reagent are coupled or that the detected analytes are in an amount that is less than $1x10^6$.

However, Kaplan teaches a method wherein an analyte of interest in one or more cells or particles is detected (column 1, lines 64-67). The method retains the cells by binding the cells to magnetic particles that are further coupled (i.e., conjugated) to tyramide (column 13, lines 15-50). Tyramide then couples to a labeling agent (i.e., detectable marker; column 3, lines 40-60); thus, the labeling agent is indirectly coupled to the first targeting species via the tyramide. Kaplan et al also teach detecting analytes that are present at less than 20,000 molecules/cell (or particle), which has the added advantage of detecting analytes that do not have to be overexpressed in a cell (i.e., the analytes are at their normal level in the cell; column 2, lines 15-25). Thus, Kaplan teaches the known technique of detecting analytes that are in an amount that is less than $1x10^6$ per particle and the coupling of the labeling reagent.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method as taught by Hansen et al so that the first targeting species (i.e., magnetic particles) is indirectly conjugated to a labeling agent (via tyramide) and so that the detected analytes are in an amount that

is less than $1x10^6$ per particle as taught by Kaplan to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of allowing detection of analytes at their normal level in the cell (because the detected analytes do not have to be overexpressed in a cell) as explicitly taught by Kaplan (column 2, lies 15-25). In addition, it would have been obvious to the ordinary artisan that the known technique of detecting analytes that are in an amount that is less than $1x10^6$ per particle using the coupling of the labeling reagent as taught by Kaplan could have been applied to the method of Hansen et al with predictable results because the known technique of detecting analytes that are in an amount that is less than $1x10^6$ per particle using the coupling of the labeling reagent as taught by Kaplan predictably results in detection of analytes within a cell.

Regarding claim 88, the method of claim 87 is discussed above. Hansen et al teach the particle is a cell (paragraph 0007).

Regarding claim 89, the method of claim 88 is discussed above. Kaplan teaches the analyte is in or on the surface of a particle (column 4, lines 35-60). The particle is a non-cellular solid particle (column 3, lines 30-35), which is interpreted as a solid phase particle, which is taught by Kaplan to include beads (column 8, lines 15-25). Thus, modification of the method of Hansen et al with the teachings of Kaplan results in a method using beads as particles.

Regarding claim 90, the method of claim 87 is discussed above. Hansen et al also teach the analyte is DNA (paragraph 0007).

Regarding claim 91, the method of claim 88 is discussed above. Kaplan further teaches the protein is MHC class I (column 4, lines 35-60), which is a membrane bound protein, as evidenced by Smith et al (page 2035). Thus modification of the method of Hansen et al with the teachings of Kaplan results in analytes that are membrane bound proteins.

Regarding claim 92, the method of claim 88 is discussed above. Hansen et al further teach the analyte is DNA, which is in a cell (paragraph 0007).

Regarding claims 95-96, the method of claim 87 is discussed above. Kaplan teaches the analyte is present at less than 20,000 molecules/cell (or particle; column 2, lines 15-25). Thus, modification of the method of Hansen et al with the teachings of Kaplan results in a method wherein the analyte is present in an amount between 500 and 50,000 molecules (i.e., claim 96), which is less than $5x10^5$ analyte detectable positions (i.e., claim 95).

Regarding claim 97, the method of claim 87 is discussed above. Hansen et al also teach the alternate embodiment wherein the cells are yeast cells (paragraph 0012).

Regarding claim 98, the method of claim 87 is discussed above. Hansen et al teach the cells are blood cells (paragraph 0012).

Regarding claim 99, the method of claim 87 is discussed above. Hansen et al also teach the liquid material comprises at least two different species of particles (paragraph 0240).

Regarding claim 101, the method of claim 87 is discussed above. Hansen et al also teach binding at least two distinct targeting species to at least two distinct species

of analyte; namely, two different particles interacting with two different molecules (paragraph 0234). In addition, Kaplan teaches binding at least two distinct targeting species to at least two distinct species of analyte and labeling the at least two distinct targeting species with two distinct labeling agents; namely, a more than one analyte is detected by using a first binding partner specific for a first analyte of interest, a second binding partner with enzymatic activity and which specifically binds to the first binding partner, a substrate for the enzymatic activity of the second binding partner, and a labeling molecule containing tyramide, followed by contacting with a third binding partner specific for a second analyte of interest, a fourth binding partner with enzymatic activity and which specifically binds to the third binding partner, a substrate for the enzymatic activity of the fourth binding partner, and a labeling molecule containing tyramide and specific for the fourth binding partners (column 6, lines 30-55). Thus, modification of the method of Hansen et al with the teachings of Kaplan results in a method comprising binding at least two distinct targeting species to at least two distinct species of analyte and labeling the at least two distinct targeting species with two distinct labeling agents.

Regarding claims 102 and 130, the method of claim 87 is discussed above. Kaplan also teaches the analyte is a Cluster of Differentiation marker (i.e., claim 102); namely, CD45 (column 4, lines 35-60 and Example 2).

Regarding claim 107, the method of claim 87 is discussed above. Kaplan also teaches the analyte is a marker of disease; namely, a disease is determined via the method (column 8, lines 35-80). Thus, modification of the method of Hansen et al with

the teachings of Kaplan results in a method wherein the at least one species of analyte is a medical marker of a disease.

Regarding claim 108, the method of claim 87 is discussed above. Hansen et al also teach more than one first targeting species, each of said more than one first targeting species being directed to a different analyte; namely, two different particles interacting with two different molecules (paragraph 0234). In addition, Kaplan teaches the reagent material comprises more than one first targeting species, each of said targeting species being directed to a different analyte; namely, a more than one analyte is detected by using a first binding partner specific for a first analyte of interest and a third binding partner specific for a second analyte of interest (column 6, lines 30-55). Thus, modification of the method of Hansen et al with the teachings of Kaplan results in a method comprising reagent material comprising more than one first targeting species, each of said targeting species being directed to a different analyte.

Regarding claim 110, the method of claim 87 is discussed above. Kaplan teaches the targeting species is a nucleotide probe complementary to a sequence of an analyte species; namely, the analyte is a nucleic acid, which binds to a binding partner that is also a nucleic acid (column 3, line 65-column 4, lines 60). Thus, modification of the method of Hansen et al with the teachings of Kaplan results in a method comprising a targeting species that is a nucleotide probe complementary to a sequence of an analyte species.

Regarding claims 112 and 137, the method of claim 87 is discussed above. Hansen et al teach the liquid material is blood (paragraph 0012).

Regarding claim 114, the method of claim 87 is discussed above. Kaplan teaches the reagent material is a fluorescently labeled nucleotide probe; namely, the analyte is a nucleic acid, which binds to a fist binding partner that is also a nucleic acid (column 3, line 65-column 4, lines 60), and the first binding partner is labeled with tyramide (column 11, lines 1-30), which has a fluorescent label thereon (column 13, lines 30-40). Thus, modification of the method of Hansen et al with the teachings of Kaplan and results in a method comprising a reagent material that is a fluorescently labeled nucleotide probe.

Regarding claims 116 and 138, the method of claim 87 is discussed above. Kaplan teaches the labeling agent is the fluorescence amplification agent fluorescyl-tyramine; namely, tyramine is conjugated to form tyramide (column 11, lines 1-32), and the tyramide is conjugated to fluorescein (column 13, lines 20-50). Thus, modification of the method of Hansen et al with the teachings of Kaplan and results in a method comprising a reagent material comprising the fluorescence amplification agent fluorescyl-tyramine.

Regarding claims 117-118, the method of claim 87 is discussed above. Kaplan teaches the dye is the cyanine dye Cy3.29 (i.e., claims 117-118; column 1, lines 45-55). Thus, modification of the method of Hansen et al with the teachings of Kaplan and results in a method comprising a reagent material comprising a cyanine dye.

Regarding claim 120, the method of claim 87 is discussed above. Hansen et al teach the image is recorded using an array of detection devices; namely, an array of detection device is used (Abstract), and a recording is produced (e.g., Figure 11A).

Regarding claim 121, the method of claim 87 is discussed above. Hansen et al teach the image is recorded using an array of detection devices; namely, a CCD device is used (Abstract), and a recording is produced (e.g., Figure 11A).

Regarding claim 122, the method of claim 87 is discussed above. Hansen et al teach the image is recorded so that the linear image on the array of detection element is equal to the original linear dimension in the exposing domain (paragraph 0064; and a recording is produced ---e.g., Figure 11A).

Regarding claim 123, the method of claim 87 is discussed above. Hansen et al teach the enlargement ratio is below 10 (paragraph 0026).

Regarding claim 124, the method of claim 87 is discussed above. Hansen et al teach substantially one exposure (Abstract), and a recording is produced (e.g., Figure 11A). Hansen et al define "substantially one exposure" as encompassing only one exposure (paragraph 0026).

Regarding claims 125-126, the method of claim 87 is discussed above. Hansen et al teach substantially one exposure (Abstract), and a recording is produced (e.g., Figure 11A). Hansen et al define "substantially one exposure" as encompassing two exposures (i.e., claim 125; paragraph 0064). Because more than one exposure is takes, and because the number of particles is assessed (i.e., quantity parameters; Abstract), the assessment of the number of particles (i.e., counting; paragraph 0054) is based on more than one image (i.e., claim 126).

Regarding claim 127, the method of claim 125 is discussed above. Hansen et al also teach changes in the image in the course of time is used in the assessment of the

number of particles; namely, repeated measurements (i.e., at different times) are taken to improve signal to noise conditions (paragraph 04220. Thus, the counting of the particles (paragraph 0054). Is based on more than one image over the course of time.

Regarding claim 129, the method of claim 87 is discussed above. Hansen et al also teach the image is recorded (e.g., Figure 11A), and that a first surface of the sample is exposed to a first light source in the form of a lamp, wherein the fluorescence signal from the first surface is focused, using a lens as a focusing means, onto a first detection means comprising a first detector (i.e., a CCD). Example 1. The first surface is the surface of the sample compartment of Example 1.

Regarding claim 139, the method of claim 118 is discussed above.

The courts have stated:

> similar properties may normally be presumed when compounds are very close in structure. Dillon, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also In re Grabiak, 769 F.2d 729, 731, 226 USPQ 870, 871 (Fed. Cir. 1985) ("When chemical compounds have very close' structural similarities and similar utilities, without more a prima facie case may be made."). Thus, evidence of similar properties or evidence of any useful properties disclosed in the prior art that would be expected to be shared by the claimed invention weighs in favor of a conclusion that the claimed invention would have been obvious. Dillon, 919 F.2d at 697-98, 16 USPQ2d at 1905; In re Wilder, 563 F.2d 457, 461, 195 USPQ 426, 430 (CCPA 1977); In re Linter, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972) (see MPEP 2144.08(d)).

The courts have also stated:

> [c]ompounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH2- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. In re Wilder, 563 F.2d 457, 195 USPQ 426 (CCPA 1977). See also In re May, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978) (stereoisomers prima facie obvious) (see MPEP 2144.09).

Therefore, the substitution of a Cy3, Cy5, or Cy5.5 dye for the Cy 3.29 dye of Kaplan would be considered an obvious variation over the prior art.

Regarding claim 140, the method of claim 87 is discussed above. Hansen et al teach the ratio of the linear dimensions is equal to no more than 4 (paragraph 0064).

8. Claims 93, 103, 110-111, and 114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) in view of in view of Kaplan (U.S. Patent No. 6,280,961 B1, issued 28 August 2001) as applied to claims 87-88 and 92 above, and further in view of Singer et al (U.S. Patent No. 5,728,527, issued 17 March 1998).

It is noted that while claims 110 and 114 have been rejected under 35 U.S.C 103(a) as described above in Section 7, the claims are also obvious using the interpretation outlined below.

Regarding claims 93, 103, 110-111, and 114, the method of claims 87-88 and 92 is discussed above in Section 7.

Hansen et al teach binding a fluorochrome to DNA (i.e., the analyte) within a somatic cell (i.e., claim 92; paragraph 0143). DNA in a somatic cell is inside the nucleus, which is an organelle (i.e., claim 93). Kaplan also teaches the analyte is a nucleic acid (column 4, lines 35-55), that the analyte is present at less than 20,000 molecules/cell (or particle; column 2, lines 15-25), and that the analyte is in a cell (column 4, lines 35-60).

However, neither Kaplan nor Hansen et al specifically teach the analyte is a chromosomal DNA sequence (i.e., claim 103). Chromosomal DNA sequences within a cell are inside the nucleus, which is an organelle (i.e., claim 93). Probes that bind

chromosomal DNA sequences within a cell are in situ hybridization probes (i.e., claim 111), and are a targeting species that is a nucleotide probe complementary to a sequence of an analyte species (i.e., claim 110).

However, Singer et al teach in situ hybridization probes (i.e., claim 111), which bind to specific sequences on chromosomal DNA (i.e., claim 103; column 2, lines 19-45) and are nucleotide probes complementary to a sequence of an analyte species (i.e., claim 110). Chromosomal DNA sequences are inside the nucleus, which is an organelle (i.e., claim 93) inside a cell. The oligonucleotide probes are fluorescently labeled (column 1, lines 50-67). Singer et al further teach in situ hybridization probes have the added advantage of determining the expression level of genes during specific developmental stages (i.e., larval and embryonic stages; column 2, lines 19-45). Thus, Singer et al teach the known technique of detection chromosomal DNA within an organelle that is within a cell using in situ hybridization probes.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes in cells as taught by Hansen et al in view of Kaplan so that the detection is of chromosomal DNA sequences using in situ hybridization probes as taught by Singer et al to arrive at the instantly claimed invention with a reasonable expectation of success. The modification would result in a method using in situ hybridization probes (i.e., claim 111), which are a targeting species that is a nucleotide probe complementary to a sequence of an analyte species (i.e., claim 110) and is fluorescently labeled (i.e., claim 114), to bind to specific sequences on chromosomal DNA (i.e., claim 103), which

are inside an organelle in the form of the nucleus within the cell (i.e., claim 93). The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of allowing determination of the expression level of genes during specific developmental stages as explicitly taught by Singer et al (column 2, lines 19-45). In addition, it would have been obvious to the ordinary artisan that the known technique of using the in situ hybridization probes as taught by Singer et al could have been applied to the method of Hansen et al in view of Kaplan with predictable results because the known technique of using the in situ hybridization probes as taught by Singer et al predictably results in reliable detection of sequences within cellular analytes.

9. Claim 94 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) in view of in view of Kaplan (U.S. Patent No. 6,280,961 B1, issued 28 August 2001) as applied to claims 87-88 and 92 above, and further in view of Connors et al (U.S. Patent No. 5,726,009, issued 10 March 1998).

Regarding claim 94, the method of claims 87-88 and 92 is discussed above in Section 7.

Neither Kaplan nor Hansen et al teach the analyte is on the surface of an organelle (i.e., claim 94).

However, Connors et al teach the detection of an analyte on the surface of an organelle; namely, a targeting species/labeling agent in the form of a dye binds to the

nuclear membrane. The nuclear membrane is the surface of the nucleus, which is an organelle and is comprised in a cell (column 6, lines 9-30). Thus, the analyte is the nuclear membrane, which is located on the surface of the organelle (i.e., claim 94). Connors et al also teach the detection of the nuclear membrane (i.e., as an analyte) has the added advantage of identifying dead cells, thereby allowing determination of the number of viable cells in a population (column 6, lines 9-30). Thus, Connors et al teaches the known technique of detecting an analyte on the surface of an organelle.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes within cells as taught by Hansen et al in view of Kaplan so that the analyte detected in and analyte on the surface of an organelle as taught by Connors et al with a reasonable expectation of success. The modification would result in a method that detects the nuclear membrane, which is on the surface of an organelle (i.e., claim 94). The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of allowing determination of the number of viable cells in a population by identifying dead cells as explicitly taught by Connors et al (column 6, lines 9-30). In addition, it would have been obvious to the ordinary artisan that the known technique of detecting an analyte on the surface of an organelle in a cell as taught by Connors et al could have been applied to the method of Hansen et al in view of Kaplan with predictable results because the known technique of detecting an analyte on the surface of an organelle in a

cell as taught by Connors et al predictably results in reliable detection of analytes within cells.

10. Claims 100, 109, 113, 115, and 128 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) in view of in view of Kaplan (U.S. Patent No. 6,280,961 B1, issued 28 August 2001) as applied to claims 87 and 99 above, and further in view of Lea et al (U.S. Patent No. 5,428,451, issued 27 June 1995).

Regarding claims 100, 109, 113, and 115, the method of claims 87 and 99 is discussed above in Section 7.

Kaplan teaches antibodies (i.e., claims 109 and 113; Example 1), the addition of fixing agents (column 2, lines 55-67), and that the cells are tissue cells (i.e., claim 115; column 3, lines 10-30). Thus, modification of the method of Hansen et al with the teachings of Kaplan results in the use of antibodies and fixing agents on tissue cells.

Neither Hansen et al nor Kaplan specifically teach the other limitations of the instant claims.

However, Lea et al teach a method for assessing at least one quality or quantity parameter of a particle in a liquid material utilizing a liquid material (i.e., fluid) comprising particles (column 2, lines 19-35). The particles are blood cells (column 4, lines 25-45). The particles are bound to reagents in the form of superparamagnetic beads (i.e., particles), which selectively and directly bind an analyte position of said species of analyte because the magnetic beads are attached to selected cells by

specific monoclonal antibodies (column 4, line 25-column 5, line 5). The antibodies are a first targeting species. The beads are also attached via direct coupling to a fluorescent labeling agent via a sandwich complex (column 4, line 25-column 5, line 5). Fluorescent labels absorb and emit electromagnetic radiation in the form of light to generate a detectable electromagnetic signal. The fluid containing the particles is then passed through an

Lea et al teach only one of the species of particles has bound thereto or comprised therein the species of analyte; namely, the particles of interest are bound to reagents in the form of superparamagnetic beads (i.e., particles), which selectively and directly bind an analyte position of said species of analyte because the magnetic beads are attached to selected cells by specific monoclonal antibodies (column 4, line 25-column 5, line 5). Because antibodies are highly specific, the antibodies bind only to one type of cell (i.e., particle) in the sample; namely, only to the cells having the analyte to which the antibodies bind (i.e., claim 100).

Lea et al further teach the targeting species is an antibody to the analyte species; namely, the targeting species is the monoclonal antibody on the magnetic bead (i.e., claim 109; column 4, line 25-column 5, line 5).

Lea et al also teach the reagent material is an antibody labeled with a reactive moiety; namely, the reagent material is the bead having the antibody thereon, which is then reagent with an optical label in the form of a fluorescent dye (column 4, line 25-column 4, line 5). Because the dye reacts with the antibody/bead, the antibody is labeled with a reactive moiety; i.e., the group that reacts with the dye (claim 113).

Lea et al also teach the addition of lysing agents (i.e., claim 115; column 4, lines 55-65).

While the cited prior art does not teach the lysing agents are added with the targeting species/labeling agent as part of the reagent material, the courts have held that selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results (*In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946). See MPEP 2144.04 IV.C. Thus, modification of the method of Hansen et al with the teachings of Kaplan and Lea et al results in a method comprising lysing reagents and tissue fixing agents (i.e., claim 115).

Lea et al also teach the antibody staining methods have the added advantage of allowing specific selection of cells via binding of the antibodies (column 4, line 25-column 5, line 5). Thus, Lea et al teach the known techniques of using the limitations of the instant claims.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes using antibodies as taught by Hansen et al in view of Kaplan so that antibodies and lysing agents are used in accordance with the teachings of Lea et al to arrive at the methods of the instant claim with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modifications because said modifications would have resulted in a method having the added advantage of allowing specific selection of cells via binding of the antibodies as explicitly taught by Lea et al (column 4, line 25-column 5, line 5). In addition, it would have been obvious to

the ordinary artisan that the known techniques taught by Lea et al could have been applied to the method of Hansen et al in view of Kaplan with predictable results because the known techniques taught by Lea et al predictably result in reliable binding to and detection cells as well as proper sample processing (i.e., via use of lysing agents).

Regarding claim 128, the method of claim 87 is discussed above.

Neither Hansen et al Kaplan, nor Lea et al explicitly teach a distinction between at least two spectral properties of a labeling agent is used to obtain at least one quality or quantity parameter of the particles as an embodiment of the invention of Lea et al.

However, Lea et al do teach distinction between at least two spectral properties of a labeling agent is used to obtain at least one quality or quantity parameter of the particles; namely, the spectral properties of light scattering and fluorescence of the particles are measured, which has the added advantage of providing information on the surface structure of the particles (i.e., cells) as well as provide information about the fluorescent labels themselves (column 1, lines 30-41). Thus, Lea et al teach the known technique of measuring a distinction between at least two spectral properties of a labeling agent.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on cells (i.e., microparticles) as taught by Hansen et al in view of Kaplan so that the method uses at least two spectral properties of a labeling agent to obtain at least one quality or quantity parameter of the particles as taught by Lea et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary

artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of providing information on the surface structure of the particles as well as provide information about the fluorescent labels themselves as explicitly taught by Lea et al (column 1, lines 30-41). In addition, it would have been obvious to the ordinary artisan that the known technique taught by Lea et al could have been applied to the method of Hansen et al in view of Kaplan with predictable results because the known techniques taught by Lea et al predictably results in providing information on both the surface structure of the particles (i.e., cells) and the fluorescent labels themselves.

11. Claims 102, 104, 107, and 131-132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) in view of in view of Kaplan (U.S. Patent No. 6,280,961 B1, issued 28 August 2001) as applied to claim 87 above, and further in view of Riabowol (U.S. Patent No. 5,877,161, issued 2 March 1999).

It is noted that while claims 102 and 107 have been rejected as described in Section 7 above, claims are also obvious using the alternative interpretation outlined below.

Regarding claims 102, 104, 107, and 131-132, the method of claim 87 is discussed above in Section 7.

Neither Kaplan nor Hansen et al teach detection of a cell cycle related protein (i.e., claims 102 and 104); namely, cyclin D1 (i.e., claims 131-132), which is a cell cycle

protein (i.e., claims 102 and 104) that is a that is a medical marker of a disease (i.e., claim 107).

However, Riabowol teaches detection of cyclin D1, which has the added advantage of allowing detection of a state of quiescence, hyperplasticity, or neoplasia in a biological sample (column 4, lines 1-16). Thus, Riabowol teaches the know technique of detecting cyclin D1.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on or within cells as taught by Hansen et al in view of Kaplan so that the analyte detected is the cell cycle protein cyclin D1 (i.e., claims 102, 104, and 131-132), which is a marker of a disease (e.g., neoplasia; claim 107) as taught by Riabowol to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of allowing detection of a state of quiescence, hyperplasticity, or neoplasia in a biological sample as explicitly taught by Riabowol (column 4, lines 1-16). In addition, it would have been obvious to the ordinary artisan that the known technique of detecting the cell cycle protein cyclin D1 as taught by Riabowol could have been applied to the method of Hansen et al in view of Kaplan with predictable results because the known technique of detecting the cell cycle protein cyclin D1 as taught by Riabowol predictably results in reliable detection of neoplasia within cells.

12. Claims 105, 107, and 135 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) in view of in view of Kaplan (U.S. Patent No. 6,280,961 B1, issued 28 August 2001) as applied to claim 87 above, and further in view of Draetta et al (U.S. Patent No 5,691,147, issued 25 November 1997).

It is noted that while claim 107 has been rejected as described above in Sections 7 and 11 above, the claim is also obvious using the alternative interpretation outlined below.

Regarding claims 105, 107, and 135, the method of claim 87 is discussed above in Section 1.

Neither Kaplan nor Hansen et al teach detection of the cell cycle related protein receptor (i.e., claim 105); namely, CDK4, which is a medical marker of a disease (i.e., claim 107) and is a cyclin dependent kinase (i.e., claim 135).

However, Draetta et al teach the detection of the level of CDK4 in a binding assay (column 25, line 65-column 26, line 35), wherein CDK4 is strongly implicated in the control of cell proliferation during the G1 phase (i.e., claims 105 and 135; column 1, lines 2-42). Determination of cell proliferation aids in the determination of the risk of certain disorders in humans (i.e., claim 107; column 3, lines 50-55). Thus, Draetta et al teach the known technique of detection CDK4.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on or within cells as taught by Hansen et al in view of Kaplan so that the

detected analyte is the a cell cycle related protein receptor CDK4 (i.e., claims 105 and 135), which is a marker of a disease (i.e., claim 107) as taught by Draetta et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of aiding in the determination of the risk of certain disorders in humans by determination of the amount of cell proliferation as explicitly taught by Draetta et al (column 1, lines 2-42 and column 3, lines 50-55). In addition, it would have been obvious to the ordinary artisan that the known technique of detecting CDK4 as taught by Draetta et al could have been applied to the method of Hansen et al in view of Kaplan with predictable results because the known technique of detecting CDK4 as taught by Draetta et al predictably results in reliable detection of certain disorders within human cells.

13. Claims 106, 107, and 136 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) in view of in view of Kaplan (U.S. Patent No. 6,280,961 B1, issued 28 August 2001) as applied to claim 87 above, and further in view of Bitler et al (U.S. Patent No. 6,379,882 B1, issued 30 April 2002).

It is noted that while claim 107 has been rejected as described above in Sections 7 and 11-12 above, the claim is also obvious using the alternative interpretation outlined below.

Regarding claims 106, 107, and 136, the method of claim 87 is discussed above in Section 7.

Neither Kaplan nor Hansen et al teach detection of a marker of apoptosis (i.e., claim 106); namely, Annexin V (i.e., claim 136), which is a medical marker of a disease (i.e., claim 107).

However, Bitler et al teach detection of phosphatidylserines targeted with Annexin V, which has the added advantage of allowing quantitation of apoptotic cells (column 12, lines 31-54). Thus, Bitler et al teach the known technique of detection of phosphatidylserines targeted with Annexin V.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on or within cells as taught by Hansen et al in view of Kaplan so that the analyte detected is phosphatidylserines targeted with Annexin V as taught by Bitler et al to arrive at the instantly claimed invention with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of allowing quantitation of apoptotic cells as explicitly taught by Bitler et al (column 12, lines 31-54). In addition, it would have been obvious to the ordinary artisan that the known technique of detecting phosphatidylserines targeted with Annexin V as taught by Bitler et al could have been applied to the method of Hansen et al in view of Kaplan with predictable results because the known technique of detecting phosphatidylserines

targeted with Annexin V as taught by Bitler et al predictably results in reliable detection of apoptotic cells.

14. Claim 119 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) in view of in view of Kaplan (U.S. Patent No. 6,280,961 B1, issued 28 August 2001) as applied to claim 87 above, and further in view of Mathies et al (U.S. Patent No. 6,100,535, issued 8 August 2000).

Regarding claim 119, the method of claim 87 is discussed above in Section 7.

While Hansen et al teach a recording is produced (e.g., Figure 11A), focusing using an optical system, and scanning (paragraphs 0035-0037), neither Kaplan nor Hansen et al teach the recording of the image comprises the use of a confocal scanner.

However, Mathies et al teach the use of confocal scanners, which have the added advantage of permitting high sample rates with simultaneous detection of multiple colors of fluorescent signals (column 5, lines 10-16). Thus, Mathies et al teach the known technique of using a confocal scanner.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising recording detection of analytes on or within cells as taught by Hansen et al in view of Kaplan by using a confocal scanner to record the image as taught by Mathies et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said

modification would have resulted in a method having the added advantage of permitting high sample rates with simultaneous detection of multiple colors of fluorescent signals as explicitly taught by Mathies et al (column 5, lines 10-16). In addition, it would have been obvious to the ordinary artisan that the known technique of using a confocal scanner to record the image as taught by Mathies et al could have been applied to the method of Hansen et al in view of Kaplan with predictable results because the known technique of using a confocal scanner to record the image as taught by Mathies et al predictably results in reliable method of recording images.

15. Claims 102, 104-105, 107, 131, and 133 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) in view of in view of Kaplan (U.S. Patent No. 6,280,961 B1, issued 28 August 2001) as applied to claim 87 above, and further in view of Sherley et al (U.S. Patent No. 5,741,646, issued 21 April 1998).

It is noted that while claim 102 is rejected as described above in Sections 7 and 11, claim 104 is rejected as described above in Section 11, claim 105 is rejected as described above in Section 12 above, claim 107 is rejected as described in Sections 7 and 11-13, and claim 131 is rejected as described above in Section 11 above, the claims are also obvious using the alternate interpretation detailed below.

Regarding claims 102, 104-105, 107, 131, and 133, the method of claim 87 is discussed above in Section 7.

Neither Kaplan nor Hansen et al teach detection of p53 (i.e., claim 133), which is a tumor suppressor protein (i.e., claim 131), a cell cycle related protein (i.e., claims 102 and 104), a cell cycle related protein receptor (i.e., claim 105), and an indicator of disease (i.e., claim 107).

However, Sherley et al teach the detection of p53 (column 8, lines 40-60), wherein detection of p53 has the added advantage of aiding in the diagnosis of disease that are due to changes in cell proliferative capacity (column 2, lines 40-55). Thus, Sherley et al teach the known technique of detecting p53.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising recording detection of analytes on or within cells as taught by Hansen et al in view of Kaplan so that the analyte detected is p53 (i.e., claim 133), which is a tumor suppressor protein (i.e., claim 131), a cell cycle related protein (i.e., claims 102 and 104), a cell cycle related protein receptor (i.e., claim 105), and an indicator of disease (i.e., claim 107), as taught by Sherley et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of aiding in the diagnosis of disease that are due to changes in cell proliferative capacity as explicitly taught by Sherley et al (column 2, lines 40-55). In addition, it would have been obvious to the ordinary artisan that the known technique of detecting p53 as taught by Sherley et al could have been applied to the method of Hansen et al in view of Kaplan with predictable results because the known technique of

detecting p53 as taught by Sherley et al predictably results in detection of a molecule known to be involved in diseases caused by alteration of cellular proliferation.

16. Claims 102, 104-105, 107, and 134 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al (European Patent Application No. EP 1 180 675 A2, published 20 February 2002) in view of in view of Kaplan (U.S. Patent No. 6,280,961 B1, issued 28 August 2001) as applied to claim 87 above, and further in view of Harvey et al (U.S. Patent No. 5,344,760, issued 6 September 1994).

It is noted that while claim 102 is rejected as described above in Sections 7, 11, and 15, claim 104 is rejected as described above in Sections 11 and 15, claim 105 is rejected as described above in Sections 12 and 15 above, and claim 107 is rejected as described in Sections 7, 11-13, and 15, the claims are also obvious using the alternate interpretation detailed below.

Regarding claims 102, 104-105, 107, and 134, the method of claim 87 is discussed above in Section 9.

Neither Hansen et al nor Kaplan teach detection of epidermal growth factor receptor (i.e., claim 134), which is a cell cycle related protein (i.e., claims 102 and 104), or a cell cycle related protein receptor (i.e., claim 105).

However, Harvey et al teach the detection of EGFR (Abstract and column 3, lines 25-40), which has the added advantage of aiding in the investigation of tumors (column 3, lines 25-50). Thus, Harvey et al teach the known technique of detecting EGFR.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising recording detection of analytes on or within cells as taught by Hansen et al in view of Kaplan so that the analyte detected is EGFR (i.e., claim 134), which is a cell cycle related protein (i.e., claims 102 and 104), a cell cycle related protein receptor (i.e., claim 105), and an indicator of disease (i.e., claim 107), as taught by Harvey et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of aiding in the investigation of tumors as explicitly taught by Harvey et al (column 3, lines 25-50). In addition, it would have been obvious to the ordinary artisan that the known technique of detecting EGFR as taught by Harvey et al could have been applied to the method of Hansen et al in view of Kaplan with predictable results because the known technique of detecting EGFR as taught by Harvey et al predictably results in detection of a molecule known to be present in tumors.

Response to Arguments

17. Applicant's arguments filed 5 May 2010 (hereafter the "Remarks" have been fully considered but they are not persuasive for the reasons discussed below.

A. Applicant argues on pages 14-15 of the Remarks that Cy3, Cy5, and Cy5.5 are not trademarks, based on the wikipedia citations (included by the examiner on the Form 892 included with this Office Action),

However, the information regarding Genetix trademarks provided by the Genetix website clearly states that Cy3, Cy5, and Cy5.5 are third party trademarks of GE Healthcare ([retrieved on 2010-07-20]. Retrieved from the Internet: <URL:www.genetix.com/en/trademarks.index.html; >). Thus, the rejection is maintained.

B. It is noted that Applicant's arguments, as well as the Declaration of Rolf Henrik Berg (hereafter "the Declaration"), refer to the previous rejections of the claims, and particularly address the alleged hydrodynamic methods of Lea et al. These arguments and the Declaration have been considered but are moot in view of the new ground(s) of rejection necessitated by the amendments. However, arguments still relevant to the rejections above are considered below.

C. With respect to Lea et al, it is noted that in the instant rejections Lea et al is merely relied upon for known techniques regarding the use of antibodies for binding to cells, the use of fixing agents, and the distinction between at least two spectral properties of a labeling agent. Standstill detection (i.e., a hydrostatic method) is taught by Hansen et al as discussed above. The flow cytometry and hydrodynamic methods of Lea et al are no longer relied upon.

Thus, while the Declaration under 37 CFR 1.132 filed 4 May 2010 is sufficient to overcome the previous rejections of the claims based upon the arguments regarding Lea et al, the arguments in the Remarks and the Declaration concerning hydrodynamic methods are moot in view of the new rejections **necessitated by the amendments**.

D. Applicant argues on pages 27-28 of the Remarks that Singer et al cannot be combined because Singer et al does not use particles as a first targeting species.

However, Singer et al teach a first targeting species in the form of an in situ hybridization probe, which is labeled, and thus is coupled either directly or indirectly to the labeling species as discussed above. Thus, the prior art particles are not needed as the first targeting species.

In addition, Kaplan teaches the analyte is in the cell and is a nucleic acid (column 4, lines 35-60). Thus, Kaplan teaches the method of detection encompasses detection of nucleic acids in cells.

E. Applicant argues on pages 28-29 of the Remarks that there is no expectation of success. Applicant provides no evidence to support this argument.

However, as noted above, Singer et al teach a first targeting species in the form of an in situ hybridization probe, which is labeled, and thus is coupled either directly or indirectly to the labeling species as discussed above. Thus, the prior art particles are not needed as the first targeting species.

Further, Singer et al specifically teach detection on chromosomes (column 1 and column 8, "Utility of the Invention").

In addition, Kaplan teaches the analyte is in the cell and is a nucleic acid (column 4, lines 35-60). Thus, Kaplan teaches the method of detection encompasses detection of nucleic acids in cells, and there is a reasonable expectation of success.

In addition, MPEP 716.01(c) makes clear that "[t]he arguments of counsel cannot take the place of evidence in the record" (*In re Schulze*, 346 F.2d 600, 602, 145 USPQ

716, 718 (CCPA 1965)). Thus, counsel's mere arguments that there is no expectation of success cannot take the place of evidence in the record.

It is noted that the Response above should not be construed as an invitation to file an after final declaration. See MPEP 715.09 [R-3].

F. Applicant argues on page 30 of the Remarks that Connors et al is incorrectly interpreted because Connors et al allegedly requires magnification.

However, the rejections do not rely upon Connors et al for the method or means of detection; rather, Connors et al is merely relied upon for an analyte on the surface of an organelle.

G. Applicant argues on pages 32-33 of the Remarks that Draetta discussed probe/primers.

However, the Abstract of Draetta et al clearly discusses **proteins** that bind CDK4. Thus, contrary to Applicant's assertions on page 33 of the Remarks, there is a reasonable expectation of success in cell surface binding to CDK4.

In addition, it is also reiterated arguments of counsel cannot take the place of evidence in the record. Thus, counsel's mere arguments that there is no expectation of success cannot take the place of evidence in the record.

It is noted that the Response above should not be construed as an invitation to file an after final declaration.

H. Applicant argues on pages 33-34 of the Remarks that Bitler et al does not apply to surface labeling because it is a cell core labeling technique.

However, Bitler et al clearly teach staining cells to with annexin as discussed above.

In addition, Kaplan teaches the analyte is in the cell and is a lipid (column 4, lines 35-60). Thus, Kaplan teaches the method of detection encompasses detection of lipids (i.e., phosphatidylserines) in cells, and there is a reasonable expectation of success.

In addition, it is also reiterated arguments of counsel cannot take the place of evidence in the record. Thus, counsel's mere arguments that there is no expectation of success cannot take the place of evidence in the record.

It is noted that the Response above should not be construed as an invitation to file an after final declaration.

l. Applicant argues that Mathies et al does not provide a reasonable expectation of success because Mathies et al teaches detection of nucleic acids.

However, it is reiterated that Kaplan teaches the analyte is in the cell and is a nucleic acid (column 4, lines 35-60). Thus, Kaplan teaches the method of detection encompasses detection of nucleic acids in cells, and there is a reasonable expectation of success.

In addition, it is also reiterated arguments of counsel cannot take the place of evidence in the record. Thus, counsel's mere arguments that there is no expectation of success cannot take the place of evidence in the record.

It is noted that the Response above should not be construed as an invitation to file an after final declaration.

J. In response to applicant's argument on page 35 that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

K. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the cited references refer to the detection of proteins in cells as discussed above. Harvey et al teach the detection of EGFR (Abstract and column 3, lines 25-40), which has the added advantage of aiding in the investigation of tumors (column 3, lines 25-50). Thus, Harvey et al teach the known technique of detecting EGFR, and the modification is obvious for the reasons discussed above.

In addition, it is also noted that the Supreme Court ruling for *KSR Int'l Co. v. Teleflex, Inc* (No 04-1350 (US 30 April 2007) forecloses the argument that a **specific**

teaching, suggestion, or motivation is required to support a finding of obviousness. See *Ex parte Smith* (USPQ2d, slip op. at 20 (Bd. Pat. App. & Interf. June 25, 2007).

L. Applicant argues on page 38 of the Remarks that Hansen et al teach DNA binding.

However, Hansen et al teach detection of analytes other than DNA (e.g., protein micelles; paragraph 0012). In addition, Kaplan teaches detection of nucleic acids, proteins, and lipids in cells (column 4, lines 35-60). Thus, Kaplan teaches the method of detection encompasses detection of nucleic acids in cells, and there is a reasonable expectation of success.

In addition, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

M. In response to applicant's argument on page 38 that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it is reiterated that that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper.

N. Applicant argues on pages 40-41 of the Remarks that the Declaration (e.g., paragraph 25 thereof) requires a very specialized chemical amplification system (ADEAS).

However, the use of a chemical amplification system is not prohibited by the claims. Indeed, the claims specifically require a first targeting species and labeling agent directly or indirectly coupled to the first targeting species. This is precisely what Kaplan teaches, including numerous embodiments wherein the first targeting species is a particle, nucleic acid, protein, or lipid which is **in the cell** as discussed above (column 4, lines 35-60). Kaplan also explicitly teaches that the tyramide coating is a result of a labeling compound comprising tyramide binding to a specific binding partner (e.g., claims 1-2 of Kaplan).

Further, any additional elements required by Kaplan (i.e., extra labels, linkers, etc) are encompassed by the open claim language "comprising" found in the instant claims.

Thus the ADEAS system of Kaplan is commensurate in scope with the claimed first targeting species and labeling agent directly or indirectly coupled to the first targeting species.

O. The Declaration also argues on paragraph 258 that Kaplan teaches away from the present invention because it suggests that the ADEAS system must be employed, but provides no evidence other than the assertion.

However, as noted above, the ADEAS system of Kaplan is commensurate in scope with the claimed first targeting species and labeling agent directly or indirectly

coupled to the first targeting species. Thus, Kaplan does not teach away from the claimed invention.

Thus, the examiner has given full consideration with respect to the Declaration, which is found unpersuasive with respect to Kaplan because Kaplan is commensurate in scope with the claims and neither the Declaration nor the Remarks provide evidence to the contrary.

It is noted that the Response above should not be construed as an invitation to file an after final declaration.

P. Applicant's remaining arguments in the Remarks refer to the hydrodynamic techniques of Lea et al, and thus are moot in view of the new rejections necessitated by the amendments (as addressed above).

Conclusion

18. No claim is allowed.

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

20. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571)272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Robert T. Crow
Primary Examiner
Art Unit 1634

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Primary Examiner, Art Unit 1634